REMARKS

Claims 1-8, 13-25 are pending. Claims 1, 2, 13, and 15 are amended. Claims 9-12 were previously cancelled.

Applicant first wishes to thank Examiner Belyavskyi and Supervisor Chan for discussing the instant invention with Applicant's representatives on January 5, 2004. As indicated by the Examiner during the telephone interview, the outstanding rejection for lack of enablement has been obviated by Applicant's amendments and remarks of November 15, 2004.

The following remarks are pursuant to the discussion of the Examiner's rejection of the claims as anticipated by Hiserodt et al. (U.S. Pat. No. 6,277,368). The Examiner will note that Applicant has amended the claims to recite specific structural attributes which further distinguish the the instant invention from the methods taught by Hiserodt et al. As a result, Applicant believes that the claims are not anticipated by Hiserodt et al. because Hiserodt et al. does not teach cytokines having the claimed structure. In addition, Applicant has amended claim 2 to specifically recite that the method of stimulating an immune response includes the step of admixing a cytokine with a cell comprising an antigen, i.e. adding an exogenous cytokine to the cell. This step of admixing is clearly not present in Hiserodt et al., and thus should render the rejection under section 102 moot as to claim 2 and its dependents. Support for these amendments is found throughout the specification, and at least at page 12, lines 10-11, page 13, lines 19-27, page 8, lines 18-19, and page 78, lines 2-6.

Structural distinctions between the instant cytokines and the cytokines taught by Hiserodt et al.

As discussed in the January 5 telephone interview, the Examiner has taken the position that, absent structural distinctions between the cytokines recited in the claims of the instant invention and those taught by Hiserodt et al, the fact that the instant claims require that the cytokine is exogenous to the cytokine-coated cell is not a patentable distinction over Hiserodt et al. In particular, the Examiner refers to the teachings of Hiserodt et al. which provide that cytokines may be endogenously expressed in a membrane-bound form as a fusion protein, wherein the "transmembrane region may be modeled on other known transmembrane proteins, or

be an artificially designed polypeptide segment with a high degree of lipophillicity" (col. 16, lines 62-65).

Contrary to the Examiner's assertions, the administered compositions recited in the claimed invention have clear structural differences compared to the transmembrane cytokines taught by Hiserodt et al. As recited in claim 1 of the instant invention, the exogenous engineered cytokines of the invention comprise a cytokine and a heterologous moiety through which said cytokine can stably bind to said cell when said engineered cytokine is admixed therewith, exogenously. That is, the engineered cytokines of the invention include as a structural element, a heterologous moiety which permits the cytokine to bind to the surface of the cell when introduced from outside the cell. There is no teaching in Hiserodt et al. of a moiety, heterologous to the cytokine, which permits the cytokine to bind to the surface of a cell when admixed exogenously therewith.

In addition, Hiserodt et al. teaches only the endogenous expression of a cytokine as a transmembrane protein, and requires that the cytokine remain stably associated in the membrane of the cell in which it is produced (col. 13, lines 19-21). Hiserodt also restricts his teaching to transmembrane sequences comprised of amino acid sequences that direct endogenously expressed proteins to the cell membrane in coordination with translation. It is well known in the art that, during expression of a transmembrane protein, such transmembrane sequences must be inserted into the membrane in a specific, energy-dependent cell biologic process that occurs in the endoplasmic reticulum, since the hydrophobic transmembrane domain *per se* is flanked on both sides by a hydrophilic stretch of amino acids (the length of which vary depending on the particular protein) that resist entry into the lipophilic membrane, stabilizing the inserted protein. See, e.g., Kendrew, The Encyclopedia of Molecular Biology, 1994, Blackwell Science, Ltd., Cambridge, MA (pages 926-930); Alberts et al., Molecular Biology of the Cell, 3rd ed., 1994, Garland Publishing, Inc., N.Y. (Chapter 12). This is the case whether the endogenously expressed transmembrane protein naturally occurs as a transmembrane protein or results from fusion with a heterologous transmembrane amino acid sequence. Given these aspects of the structure and cell biology of endogenously produced transmembrane proteins, e.g. cytokines, it is impossible to purify such a cytokine and simply admix it with a cell such that the transmembrane

sequence will insert into the cell membrane. That is, **the cytokines of Hiserodt et al. are membrane bound only because they are endogenously expressed and thus subject to specific, active cell biological processes.**

Taken together, the amendments to the claims and the foregoing remarks distinguish clearly the claimed invention over the teachings of Hiserodt et al. The instant claims are both novel and non-obvious over Hiserodt et al, and Applicant accordingly requests that the rejection be reconsidered and withdrawn.

Conclusion

It is respectfully requested that the rejections be reversed and that the claims be allowed.

Respectfully submitted,

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